REMARKS

Reconsideration is requested.

Claims 1-16 have been canceled, without prejudice.

Claims 17-29 are pending. Claim 17 has been amended, without prejudice, to further define the protein of claims 17-19.

Claims 20-29 have been added. The new claims find support throughout the specification. No new matter has been added. The claims read on the elected invention. See Office Action of June 5, 2001 and the applicants Response of September 14, 2001.

The present Examiner is the fourth Examiner assigned to the present application since filing seven (7) years ago. The present Examiner has repeated an art rejection (i.e., based on Ales (Blood, 84(10):3483-3493 (1994)) which was presented and ultimately withdrawn by a prior Examiner. The present Examiner is requested to give full faith and credit to the prior Examiner(s) Action(s). The Examiner is requested to note the following passage from MPEP § 706.04, for example:

> PREVIOUS ACTION BY DIFFERENT EXAMINER
> Full faith and credit should be given to the search and action of a previous examiner unless there is a clear error in the previous action or knowledge of other prior art. In general, an examiner should not take an entirely new approach or attempt to reorient the point of view of a previous examiner, or make a new search in the mere hope of finding something. >Amgen, Inc. v. Hoechst Marion Roussel, Inc., 126 F. Supp. 2d 69, 139, 57 USPQ2d 1449, 1499-50 (D. Mass. 2001).<

The specification has been revised to obviate the objection of same. Withdrawal of the objection to the specification is requested.

The Section 102 rejection of claims 17-19 over Ales et al (Blood, 84(10):3483-3493 (1994)), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing remarks.

The reference does not teach or suggest the method of claims 20-29.

Moreover, the reference, at best, teaches administration of a 381 amino acid sequence (i.e., the amino acid sequence codes by

> "a 1,222-bp fragment of PTX-3 (from nucleotide 36 to nucleotide 1258 according to our published sequence [i.e., Breviario,F., d'Aniello,E.M., Golay,J., Peri,G., Bottazzi,B., Bairoch,A., Saccone,S., Marzella,R., Predazzi,V., Rocchi,M. et al. Interleukin-1-inducible genes in endothelial cells. Cloning of a new gene related to C-reactive protein and serum amyloid P component, J. Biol. Chem. 267 (31), 22190-22197 (1992))]" See page 3484, right column, last paragraph of Alles et al.

The undersigned has obtained the attached (and below-listed) sequence for ACCESSION X63613 S47824 VERSION X63613.1 GI:35796 from the NCBI on-line data base which is indicated as being the nucleotide sequence, and translated protein sequence, for PTX3 from Breviario,F., et al described in Alles as being the published sequence. Neither the undersigned not the applicants have confirmed that the NCBI on-line records are correct in this regard. The Examiner has not relied on Breviario,F., et al or any sequence comparison related to Alles et al.

The above-noted and attached NCBI accession number provides the following nucleotide sequence:

```
  1 ctcaaactca gctcacttga gagtctcctc ccgccagctg tggaaagaac tttgcgtctc
 61 tccagcaatg catctccttg cgattctgtt ttgtgctctc tggtctgcag tgttggccga
121 gaactcggat gattatgatc tcatgtatgt gaatttggac aacgaaatag acaatggact
181 ccatcccact gaggacccca cgccgtgcga ctgcggtcag gagcactcgg aatgggacaa
241 gctcttcatc atgctggaga actcgcagat gagagagcgc atgctgctgc aagccacgga
301 cgacgtcctg cggggcgagc tgcagaggct gcgggaggag ctgggccggc tcgcggaaag
361 cctggcgagg ccgtgcgcgc cgggggctcc cgcagaggcc aggctgacca gtgctctgga
```

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 421 cgagctgctg caggcgaccc gcgacgcggg ccgcaggctg gcgcgtatgg agggcgcgga
 481 ggcgcagcgc ccagaggagg cggggcgcgc cctggccgcg gtgctagagg agctgcggca
 541 gacgcgagcc gacctgcacg cggtgcaggg ctgggctgcc cggagctggc tgccggcagg
 601 ttgtgaaaca gctattttat tcccaatgcg ttccaagaag atttttggaa gcgtgcatcc
 661 agtgagacca atgaggcttg agtcttttag tgcctgcatt tgggtcaaag ccacagatgt
 721 attaaacaaa accatcctgt tttcctatgg cacaaagagg aatccatatg aaatccagct
 781 gtatctcagc taccaatcca tagtgtttgt ggtgggtgga gaggagaaca aactggttgc
 841 tgaagccatg gtttccctgg gaaggtggac ccacctgtgc ggcacctgga attcagagga
 901 agggctcaca tccttgtggg taaatggtga actggcggct accactgttg agatggccac
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1081 ctgggatagt gttcttagca atgaagagat aagagagacc ggaggagcag agtcttgtca
1141 catccggggg aatattgttg ggtggggagt cacagagatc cagccacatg gaggagctca
1201 gtatgtttca taaatgttgt gaaactccac ttgaagccaa agaaagaaac tcacacttaa
1261 aacacatgcc agttgggaag gtctgaaaac tcagtgcata ataggaacac ttgagactaa
1321 tgaaagagag agttgagacc aatctttatt tgtactggcc aaatactgaa taaacagttg
1381 aaggaaagac attggaaaaa gcttttgagg ataatgttac tagactttat gccatggtgc
1441 tttcagttta atgctgtgtc tctgtcagat aaactctcaa ataattaaaa aggactgtat
1501 tgttgaacag agggacaatt gttttacttt tctttggtta attttgtttt ggccagagat
1561 gaattttaca ttggaagaat aacaaaataa gatttgttgt ccattgttca ttgttattgg
1621 tatgtacctt attacaaaaa aaatgatgaa aacatattta tactacaagg tgacttaaca
1681 actataaatg tagtttatgt gttataatcg aatgtcacgt ttttgagaag atagtcatat
1741 aagttatatt gcaaaaggga tttgtattaa tttaagacta tttttgtaaa gctctactgt
1801 aaataaaata ttttataaaa ctaaaaaaaa aaaaaaa
```

The above-noted and attached NCBI accession number provides that the following protein is translated from nucleotide base 68-1213:

```
MHLLAILFCALWSAVLAENSDDYDLMYVNLDNEIDNGLHPTEDP
TPCDCGQEHSEWDKLFIMLENSQMRERMLLQATDDVLRGELQRLREELGRLAESLARP
CAPGAPAEARLTSALDELLQATRDAGRRLARMEGAEAQRPEEAGRALAAVLEELRQTR
ADLHAVQGWAARSWLPAGCETAILFPMRSKKIFGSVHPVRPMRLESFSACIWVKATDV
LNKTILFSYGTKRNPYEIQLYLSYQSIVFVVGGEENKLVAEAMVSLGRWTHLCGTWNS
EEGLTSLWVNGELAATTVEMATGHIVPEGGILQIGQEKNGCCVGGGFDETLAFSGRLT
      GFNIWDSVLSNEEIRETGGAESCHIRGNIVGWGVTEIQPHGGAQYVS
```

At best therefore, the sequence "from nucleotide 36 to nucleotide 1258 according to our published sequence" would produce a protein of the above-listed 381 amino acid protein.

The protein of claims 17-19 is 364 amino acids.

Alles et al therefore does not teach each and every aspect of the claimed invention. The Section 102 rejection of claims 17-19 over Alles et al should be withdrawn.

Moreover, as previously successfully described to a previous Examiner, Alles fails to teach a composition of claims 17-19.

Specifically, Alles et al does not inject PTX3 in saline but rather the protein is injected with saline and toxic materials from the gel used to isolate the protein. Alles et al state the following in this regard:

> "The solubilized proteins were separated in a 10% polyacrylamide gel under reducing conditions. The gel slice containing recombinant PTX3 was excised, mechanically disrupted in saline, and injected SC into a 28-day old rabbit (Charles River, Calco, Italy)." See page 3485, left column, first paragraph of Alles et al.

It will be appreciated by one of ordinary skill in the art that the solubilized proteins separated in a 10% polyacrylamide gel under reducing conditions, and the gel slice excised, containing recombinant PTX3 which was mechanically disrupted in saline, is not a pharmaceutical composition and is rather a toxic composition injected into rabbits for producing antibodies. One of ordinary skill will appreciate that the gel slice excised, containing recombinant PTX3 contains also polyacrylamide and that polyacrylamide is neurotoxic and cannot be present in a pharmaceutical composition for human use.

The previously-submitted abstract of Zhonghua Zheng Xing Wai Ke Za Zhi 2002, Mar; 18(2):79-80, relates to an experimental study on the toxic effects of hydrophilic polyacrylamide gel.

In this abstract is reported:

> "*To study the safety of Hydrophilic* **polyacrylamide gel (HPAG)** RESULTS: It was determined that the cytotoxicity was over level-two. **The toxicity to kidney was obvious.** ...CONCLUSION: **HPAG has obvious cytotoxicity**..."" (Emphasis added).

The previously-submitted abstract of Rev. Environ. Health 1989 Jan-Dec; 8 (1-4) 3-16, relates to the Toxicity of polyacrylamide and acrylamide monomer.

In this abstract is reported:

> "... *The United States government, specifically the Food and Drug Administration and the Environmental Protection Agency, already regulates several uses of polyacrylamide; criteria and standards have been established based on numerous toxicological studies of both polyacrylamide and acrylamide. These studies are reviewed and summarized.* **The regulations generally restrict both the amount of residual acrylamide monomer in the polyacrylamide and the amount of polymer that may be used in the specified application.** *By imposing this type of restriction, a maximum limit on the amount of acrylamide in contact with food or drinking water can be indirectly achieved"* (Emphasis added).

Therefore, if a pharmaceutical composition is a mixture composed of an active ingredient and at least a pharmaceutically acceptable excipient, a mixture comprising polyacrylamide is not a pharmaceutical composition and the cited art, which contains the same, fails to anticipate the presently claimed invention.

The present Examiner notes on page 3 of the latest Office Action that:

> "A composition is a composition, regardless of its intended use. Therefore, the reference teachings anticipate the claimed invention."

The Examiner cannot however read out aspects of claims 17-19 in construing the claims. Claims 17-19 require that the compositions are pharmaceutical compositions

which contain a pharmaceutically acceptable excipient. The compositions of claims 17-19 cannot include toxic substances.

The previous and present Examiners have on the disclosure at page 3485, first full paragraph, as alleging at the point the protein was isolated in the supernatant that had DMEM in it, the claims drawn to a pharmaceutical composition were anticipated. See page 2 of the Office Action dated May 1, 2003 (Paper No. 26) and the paragraph spanning pages 2-3 of the Office Action dated October 5, 2006.

The previous Examiner relied on ATCC Catalog No. 30-2002 for the description of DMEM and the assertion that the same is "useful as an in vivo solution, thereby meeting the pharmaceutical composition limitation." Id. The present Examiner has not provided any evidence that DMEM is a pharmaceutically acceptable excipient.

The applicants again urge the Examiner to appreciate that the pending claims call for a pharmaceutically acceptable excipient. DMEM is not a pharmaceutically acceptable excipient and the Examiner is requested to consider the following in this regard.

DMEM includes the following constituents:

- CaC12 (anhydrous);
- Fe(NO3)3-9H2O;
- MgS04 (anhydrous);
- KCl;
- NaCl;
- NaHC03;
- NaH2P04*H20;
- Choline Chloride;
- Folic Acid;
- myo-Inositol;
- Nicotinamide;
- D-Pantothenic Acid (hemicalcium);
- Pyridoxine-HCl;

- Riboflavin;
- Thiamine-HCl;
- L-Arginine-HCl;
- L-Cystine-2HCl;
- L-Glutamine;
- Glycine;
- L-Histidine-HCl-H2O;
- L-Isoleucine;
- L-Leucine;
- L-Lysine.HCl;
- L-Methionine;
- L-Phenylalanine;
- L-Serine;
- L-Threonine;
- L-Tryptophan;
- L-Tyrosine-2Na-2H2O;
- L-Valine;
- D-Glucose;
- Phenol Red, Sodium Salt; and
- Sodium Pyruvate.

Among the listed constituents of DMEM are the following:

Choline Chloride, Folic Acid, Myo-Inositol, Nicotinamide, D-Pantothenic Acid (hemicalcium), Pyridoxine-HCl,Riboflavin, Thiamine-HCl, L-Arginine-HClL-Cystine-2HCl, L-Glutamine, Glicine, L-Histidine-HCl-H2O, L-Isoleucine, L-Leucine, L-Lysine.HCl, L-Methionine, L-Phenylalanine, L-Serine, L-Threonine, L-Tryptophan, Tyrosine-2Na-2H2O, L-Valine, Sodium Pyruvate.

These components will be recognized by one of ordinary skill in the art to be drug substances such that the inclusion of the same in DMEM would lead one of ordinary skill in the art to appreciate that DMEM is not a pharmaceutically acceptable excipient, as the term is generally recognized in the art.

The Examiner is requested to see in this regard, for example, the previously-submitted copy of page 48 of the Merck Manual which describes the use of Nicotinamide (also known as niacinamide) for treating pellagra. Also, the applicants previously submitted a copy of page 16611 of the Merck Manual which described the

use of folic acid for treating coronary artery disease. The Examiner is also requested to see the previously-filed excerpt from Merck's website which describes choline chloride as having a lipotropic therapeutic activity. Also the previously-filed printout from the International Program on Chemical Safety indicating that choline chloride is a nutrient and dietary supplement with therapeutic uses. The Examiner is also requested to see the previously-submitted printout from the website "suprahealth.com" indicating that folic acid has a number of therapeutic applications. Also previously-submitted was a copy of a printout from the website of "biopsychiatry.com" indicating that myo-inositol has therapeutic capacity and applications. Similarly, a printout from Blue Cross also indicates that therapeutic activity of myo-inositol. Further evidence could be provided for the other listed compounds upon the Examiner's further request. The applicants respectfully submit that, in view of the attached, DMEM is not a pharmaceutically acceptable excipient.

Beyond the above and the previously-filed evidence, and perhaps more importantly, the supernatant of the cited reference which is referred to by the Examiner and described on page 3485, first full paragraph, of Alles would not be understood by one of ordinary skill in the art to be an administerable pharmaceutical composition, as claimed. More specifically, the solution indicated by the Examiner to allegedly anticipate the presently claimed invention, would be understood by one of ordinary skill in the art to contain, for example COS cells metabolites, catabolites and residual components of the cellular lysis, such as virus related or released by the DNA of the COS cells. The applicants submit therefore that the PTX3 protein described in the cited art and relied upon by the Examiner is dissolved in a solution which, more likely than

not, may be toxic and/or infective such that the solution is not a pharmaceutically acceptable excipient and the composition is not adminsterable as a pharmaceutical composition. Accordingly, the claims are submitted to be patentable over the cited art which fails to teach each and every aspect of the presently claimed invention.

Withdrawal of the Section 102 rejection of claims 17-19 over Alles et al is requested.

The Section 103 rejection of claims 17-19 have been rejected as allegedly being obvious over Gewurz (Current Opinion in Immunology 7:54-64 (1995)) in view of U.S. Patent No. 5,426,181, is traversed. Reconsideration and withdrawal of the rejection are requested.

As has been previously noted, the cited patent fails to teach the 381 amino acid sequence of PTX3 of the present application. Specifically, the 381 amino acid sequence of the patent (sequence TSG-14 (i.e., SEQ ID NO:4) of the patent) contains Leu at position 202 whereas position 202 of the PTX3 of the present application is a Met. Moreover, the sequence of the patent is 381 amino acids in length whereas the protein of claims 17-19 of the present application is 364 amino acids in length. There is no suggestion in Gewurz or U.S. Patent No. 5,426,181, to alter the sequence of the patent to either change amino acid position 202 and to incorporate amino acids 18-381 of SEQ ID NO:1 of the present application in to the presently claimed compositions.

The claims are patentable over the combination of cited art and withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

The Examiner is requested to contact the undersigned in the event anything further is required in this regard.

Respectfully submitted,

NIXON & VANDERHYE P.C.

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LOCUS       X63613                  1837 bp    mRNA    linear   PRI 29-JUL-1993
DEFINITION  H.sapiens mRNA for pentaxin (PTX3).
ACCESSION   X63613 S47824
VERSION     X63613.1  GI:35796
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  ORGANISM  Homo sapiens
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            Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1
  AUTHORS   Breviario,F., d'Aniello,E.M., Golay,J., Peri,G., Bottazzi,B.,
            Bairoch,A., Saccone,S., Marzella,R., Predazzi,V., Rocchi,M. et al.
  TITLE     Interleukin-1-inducible genes in endothelial cells. Cloning of a
            new gene related to C-reactive protein and serum amyloid P
            component
  JOURNAL   J. Biol. Chem. 267 (31), 22190-22197 (1992)
   PUBMED   1429570
REFERENCE   2  (bases 1 to 1837)
  AUTHORS   Breviario,F.
  TITLE     Direct Submission
  JOURNAL   Submitted (03-JAN-1992) F. Breviario, Istitute Ricerche Farmacol.
            Mario Negri, Via Eritrea, 62, 20157 Milano, ITALY
COMMENT     On Aug 11, 2005 this sequence version replaced gi:258752.
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